

REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and arguments set forth is respectfully requested.

Claims 1-8 and 10-14 are pending and under consideration. Claim 1 has been amended as explained below. No new matter has been added as a result of these amendments.

Applicants thank the Examiner for stating that claim 14 is free of prior art.

Rejection of Claims 1, 2, 4-8 and 10-13 Under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 2, 4-8 and 10-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner maintains the rejection made in the previous Office Action. The Examiner provides additional comments as reiterated below. Applicants respectfully traverse this rejection.

On page 3 of the Office Action, the Examiner states "Applicants clearly have one species of the claimed genus, a mutant Bcl-2 protein consisting of 166 amino acid residues identified as SEQ ID NO: 2 comprising the replacement sequence consisting of 16 amino acid residues identified as SEQ ID NO: 1. However, Applicants assert [sic] claim to innumerable mutant Bcl-2 proteins that can contain 150 to 180 amino acid residues, wherein the replacement sequence is not limited by the type or number of acidic amino acids comprising said sequence. Likewise there is not [sic] adequate description of the flexible loop, which the replacement amino acid is to replace an undefined portion of said loop."

The Examiner asserts that the claimed mutant proteins do not provide the nexus that exists between the structure of the protein and the function. The Examiner's rejection is also based on the premise that claim 1 does not specify which isoform of the wild-type Bcl-2 the mutant protein arises from and that the specification does not describe (or claim 1 does not recite) the amino acid residues on the amino terminus and the carboxy terminus surrounding the replacement residues.

Applicants respectfully submit that the instant specification discloses a "manageable pool" of mutant proteins as claimed. First, the wild-type Bcl-2 protein which the mutant protein is derived from has a specific length of amino acids. Namely, the wild-type Bcl-2 isoforms 1-3 contain 239 amino acids. Applicants respectfully point out to the Examiner that the wild-type Bcl-2 isoforms 1-3 are identical to each other except for three amino acids shown in Figure 1 and described on page 4, lines 15-16 and page 7, lines 3-8 in the specification. The "wild-type Bcl-2 protein" is defined in the specification on page 6, lines 27-29 as specifically comprising either one of these three isoforms. Due to the Examiner's rejection as discussed below, Applicants have further amended claim 1 to recite these particular features that are known in the art. Support for this amendment can be found on page 4, lines 13-16 and Figure 1 in the specification. Applicants submit that the structure of the genus of mutant protein is finite and "manageable".

Second, in Applicants' previous Amendment, claim 1 was amended to further clarify and recite that the flexible loop of the wild-type Bcl-2 protein comprises amino acids 35-91. This feature is disclosed on page 4, line 16 and Example 1 of the specification. This feature further limits the genus of mutant protein to a genus that is finite and "manageable".

With respect to the Examiner's inquiry about the description of the amino acids on the amino terminus and the carboxy terminus surrounding the replacement sequence, the above discussion shows that they are clearly described in the specification and are clear from the claim language based on the recited amino acids 35-91.

Third, the portion of the wild-type Bcl-2 protein's flexible loop is replaced with at least 2 acidic amino acids. Applicants respectfully submit that one skilled in the art would know which amino acids are acidic (such as glutamic acid and aspartic acid). Therefore, the genus of mutant proteins is still finite and "manageable".

Page 7, lines 25-30 of the specification, clearly states that these acidic amino acids may be located at any position within the replacement sequence (the flexible loop) even though they are not limited in type (except having at least two acidic amino acids) and size. Despite this, however, the requirement that the acidic amino acids be within the replacement sequence (the flexible loop) decreases the size of the genus.

On page 8, line 19 to page 9, line 7, the specification specifically discloses that the mutant Bcl-2 proteins of the present invention do not aggregate in solution unlike the naturally occurring or wild-type Bcl-2 protein. Applicants have amended claim 1 to further recite this feature. As discussed in the specification, because of an increased content of acidic amino acids, the mutant proteins according to the present invention have specified lower isoelectric points and therefore do not aggregate in solution.

Because of all of these requirements, Applicants have sufficiently described an adequate number of members of a properly claimed genus. It is not required and not practical to disclose and claim every little change in amino acid when the genus is reasonably and credibly described in the specification.

Based on all of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-8 and 10-13 under 35 U.S.C. § 112, first paragraph, written description.

Rejection of Claims 1, 2, 4-8 and 10-13 Under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 1, 2, 4-8 and 10-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner basically reiterates her position as discussed in the Written Description rejection. Applicants have responded to the Written Description rejection above and those arguments are incorporated herein.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-8 and 10-13 under 35 U.S.C. § 112, first paragraph, enablement.

Rejection of Claims 1-8 and 10-13 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8 and 10-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner reiterates part of the rejection made in the previous Office Action as discussed below. Applicants respectfully traverse this rejection.

The Examiner maintains that the recitation "flexible loop" in claims 1, 2 and 9 is vague and indefinite. The Examiner states that the flexible loop is essential to the protein and suggests defining the loop by the amino acid residues and/or juxtaposition. Accordingly, the Examiner states that "at least a portion of a flexible loop" in claim 2 is also vague and indefinite.

Applicants' previous amendment to claim 1 clarified the flexible loop by incorporating the subject matter of claim 9 which provides the exact amino acid position of the flexible loop from a human Bcl-2 protein. Since the amino acid composition of the wild-type Bcl-2 protein is known in the art (see Figure 1), the description of the flexible loop with respect to amino acids 35-91 of the wild-type Bcl-2 protein clearly describes the amino acid residue and juxtaposition as requested by the Examiner. Applicants are confused as to why the Examiner believes that this recitation is not adequate. Applicants respectfully request the Examiner to explain her position and for her assistance if she has suggestions for alternative language that may overcome the rejection.

Regarding the Examiner's comment that the flexible loop is essential to the protein, this issue was discussed in Applicants' Amendment dated April 23, 2004. On pages 7 and 8 of that Amendment, Applicants pointed out to the Examiner that the specification teaches that the flexible loop of Bcl-X_L is not required for maintaining the integrity of the protein or retaining function (page 7, lines 2-7 of the specification). Based on sequence homology between Bcl-X_L and Bcl-2, the unstructured loop of Bcl-2 is presumed to be unnecessary for maintaining the integrity of the Bcl-2 protein (page 7, lines 7-9 of the specification).

The Examiner also objects to the recitation of the term "encode" in describing the amino acids with respect to the flexible loop. Applicants have replaced this term with "comprise".

The Examiner maintains the rejection of "at least a portion of a flexible loop" as being indefinite without reciting the number of amino acids and its function. This issue has been discussed above and those arguments are incorporated herein.

Finally, the Examiner states that "wild-type Bcl-2 protein" is indefinite because it is not clear which isoform the protein is identified for. In view of the amendments to claim 1 discussed above, this issue has been addressed by Applicants.

Additionally, Applicants would like to point out that claim 1 has been amended to fully recite "wild-type Bcl-2 protein" throughout the claim for consistency.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-8 and 10-13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection of Claims 1-8 and 10-13 Under 35 U.S.C. § 102(e) – Bennett

Claims 1-8 and 10-13 are rejected under 35 U.S.C. § 102(e), as being anticipated by Bennett *et al.*, U.S. Patent No. 6,214,986 (hereinafter "Bennett").

Specifically, the Examiner maintains the rejection made in the previous Office Action. Applicants respectfully traverse this rejection.

As pointed out in the previous Amendment, it appears that the Examiner misinterpreted Bennett's Bcl-X_L protein as being the same protein as a Bcl-2 protein. Applicants have attempted to explain that these proteins are not the same and that the fact that these proteins are different is well known to those skilled in the art. As such, Applicants pointed out to the Examiner that the Bcl-X_L protein is recited in the instant specification as SEQ ID NO: 6 (which is known in the art) and that the Bcl-2 proteins are recited in the instant specification as SEQ ID NOS: 3-5 (which are also known in the art). The Examiner, however, states that SEQ ID NOS: 3-5 are not recited in the claim and therefore Applicants' arguments are not commensurate with the scope of claim 1.

Applicants respectfully point out again to the Examiner that these terms, the structure of the Bcl-X_L protein and the structure of the Bcl-2 protein, are defined and well-known to those skilled in the art. Nevertheless, in an effort to expedite prosecution, Applicants have amended claim 1 to specifically recite SEQ ID NOS: 3-5 for the wild-type Bcl-2 isoforms. Support for this amendment can be found on page 6, lines 27-29 of the specification.

For these reasons, Applicants respectfully request withdrawal of the rejection of claims 1-8 and 10-13 under 35 U.S.C. § 102(e), as being anticipated by Bennett *et al.*, U.S. Patent No. 6,214,986.

Rejection of Claims 1-8 and 10-13 Under 35 U.S.C. § 102(b) – Thompson, Boise and Muchmore

Claims 1-8 and 10-13 are rejected under 35 U.S.C. § 102(b), as being anticipated by Thompson *et al.*, U.S. Patent No. 5,646,008 (hereinafter “Thompson”), Boise *et al.*, Cell 74: 597-608, 1993 (hereinafter “Boise”) or Muchmore *et al.*, Nature 381: 335-341, 1996 (hereinafter “Muchmore”).

The Examiner maintains these rejections made in the previous Office Action based on the same reason as provided for the art rejection citing Bennett

above. The Examiner states that the broad language of the claims reads on the amino acid sequences disclosed in Thompson, Boise or Muchmore.

Applicants respectfully traverse these rejections. Applicants' arguments above are incorporated herein.

Applicants submit that the Thompson, Boise and Muchmore references are deficient in a similar manner as Bennett. Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-8 and 10-13 under 35 U.S.C. § 102(b), as being anticipated by Thompson *et al.*, U.S. Patent No. 5,646,008, Boise *et al.*, Cell 74: 597-608, 1993 or Muchmore et al., Nature 381: 335-341, 1996

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 112 and 102. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, he/she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

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